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Hyperostosis Frontalis Interna: An Anthropological Perspective

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ABSTRACT Hyperostosis frontalis interna (HFI) is manifested by the accretion of bone on the inner table of the frontal bone. Despite the vast literature on HFI, ambiguity exists as to its etiology, osteogenesis, demography, and history. This stimulated the present broad-scale study of HFI which included the evaluation of 1,706 early 20th century skulls (1,007 males and 699 females) from the Hamann-Todd and Terry human osteological collections, as well as 2,019 pre-19th century East-Mediterranean, Amerindian, and Central European skulls. In addition, 72 cadavers were dissected for gross inspection and histology. Special attention was paid to the relationship of the brain and meninges to endocranial lesions.

HFI is an independent condition, not a symptom of a more generalized syndrome as suggested in the past. It can appear in a variety of forms but each is the result of the same process and probably of the same etiology. Investigators' previous failure to recognize the mild stages of HFI (types A and B) as an early form of the general HFI process led to erroneous statistics and interpretations of observations. HFI should also be considered a phenomenon separate from HCI, hyperostosis cranialis diffusa (HCD), and other endostoses, even when it appears in association with them. To avoid ambiguity and facilitate the description of cranial hyperostoses, uniform nomenclature (HFI, HCD) has been recommended.

HFI is rarely seen in historic populations, regardless of geographical origin. It is most commonly found among females and is believed to be associated with prolonged estrogen stimulation. While its magnitude of manifestation and frequency are much higher in females, HFI is not a purely female phenomenon. Males with hormonal disturbances such as atrophic testis were found to manifest HFI type D. HFI is associated with age insofar as it is much less frequent in females under 40 years of age. Although advanced cases of HFI (types C and D) have been observed in individuals as young as 40 years of age, it is more frequently found after age 60. The frequency of HFI type D will not increase from age 60.

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Type-predicted analysis by cohort reveals significant ethnic differences. Changes in African American (AA) females appear earlier in life and progress more rapidly than in European American (EA) females. Analysis of radiographs shows a discrepancy between the anatomic prevalence of HFI and its radiological recognition, which is very poor for mild cases. This apparently resulted in the misconceptions that HFI is entirely an old-age phenomenon, and that it is exclusively female.

Histological analysis shows that the inner table along with the closely attached dural layer play a major role in the osteogenesis of HFI. Contrary to previous models, no evidence for diploe or ectocranial plate involvement was found. Cadaver study suggests that the predilection for the frontal area may be related to an altered blood supply and/or vascular stretching. Am J Phys Anthropol 109:303–325, 1999.

Hyperostosis frontalis interna (HFI), first described by Morgagni in 1769, is a descriptive term for a specific variety of bone accretion on the inner table of the frontal bone. Two centuries later, despite extensive research, we still know very little about this phenomenon. Unfortunately, even with the great jump in medical knowledge in the last few decades, almost nothing has changed since Perou (1964) claimed that: "the mode of the development of the hyperostotic process in HCI is as obscure as its origin" (p. 76).

Previous descriptions of HFI concentrated on surface and radiological observations, leaving the etiology to conjecture (Moore, 1955; Perou, 1964). Areas of hyperostosis have occasionally been seen in other areas of the endocranium and have not always been associated with HFI (Perou, 1964).

HFI has rarely been documented in the archaeological record (e.g., Watrous et al., 1993; Stroud and Kemp, 1993; Anderson, 1993; Farwell and Molleson, 1993; Armelagos and Chrisman, 1988), despite its antiquity (Anton, 1997; Armelagos and Chrisman, 1988). In contrast, it has been demonstrated with considerable frequency in contemporary populations of postmenopausal women (Arensburg, 1989; Marlet, 1974; Hawkins and Martin, 1965; Salmi et al., 1962; Moore, 1955; Gershon-Cohen et al., 1955; Calame, 1951; Henschen, 1949; Oldberg, 1945; Eldridge and Holm, 1940; Morel, 1930). Whether HFI is unreported in the archaeological record, or if there has actually been a change in its frequency remains unclear. Is HFI a long-standing phenomenon, or is it actually a relatively new one analogous to HIV or Lyme disease? Is the perception of increased frequency related to changes in life expectancy, or is it culturally derived (e.g., fewer children, lengthening of reproductive period)?

Recognition of a disease's impact on a population is associated with how that disease is defined. The criteria selected for diagnosis are pivotal to a disease's detection. For bony involvement to be a disease criterion, for example, it must always be present. One major challenge in assessing previously reported HFI diagnoses, and in understanding the nature of the disease, relates to the accuracy of past diagnoses. To avoid possible misinterpretation, this study adopts the convention of restricting diagnostic terminology to that in current medical usage. We made an effort to investigate the full spectrum of frontal bone changes attributable to HFI and assess their relationships.

An attempt has been made to clarify the nature of HFI by providing a working definition. The following questions were addressed: 1) What is HFI? 2) What is the relationship of gender and ethnicity to HFI? 3) Is HFI age related? 4) Is there a relationship between HFI and hyperostosis cranialis diffusa (HCD)? 5) Can radiographic study provide the full spectrum of HFI and its actual frequency within a population? 6) Is HFI a modern phenomenon? 7) What is the etiology of HFI?

Previous reports on HFI (e.g., Barber et al., 1997; Arensburg, 1989; Marlet, 1974; Hawkins and Martin, 1965; Salmi et al., 1962; Moore, 1955; Gershon-Cohen et al.,

TABLE 1. Population studied by age, sex, and ethnic origin

Age group[1]	European American		African American		
	Male	Female	Male	Female	Total
20–29	26	18	69	84	197
30–39	72	41	129	84	326
40–49	121	47	96	79	343
50–59	142	53	67	58	320
60–69	123	48	46	40	257
70–79	70	65	21	30	186
80+	19	26	6	26	77
Total	573	298	434	401	1,706

[1] Age is in years.

1955; Oldberg, 1945; Eldridge and Holm, 1940) raised some of these questions without providing adequate resolution. According to Anton (1997), the difficulty in answering these questions may relate to sample bias, inadequate population size, or an overreliance on X-ray studies which tend to overlook relatively mild cases. In the present study, we attempted to overcome some of these difficulties.

MATERIALS AND METHODS

Modern skeletal populations (1,706 skulls)

Two large early 20th century skeletal collections, the Hamann-Todd Human Osteological Collection (housed at the Cleveland Museum of Natural History, Cleveland, OH) and the Terry Collection (housed at the Smithsonian Institution, Washington, DC) were used for the present study (Table 1). The distribution of all individuals examined in both collections is delineated in Table 1 according to age, sex, and ethnicity. We are aware that division of our sample population into two ethnic groups, European American and African American, may be an overgeneralization and that each of these categories may include individuals of different biological lineage. One thousand seven hundred and six midsagittal or transversely sectioned skulls (1,007 males and 699 females) were examined. This included all female skulls in the Hamann-Todd Collection. A comparison group of similar age and sex distribution was derived from the Terry Collection.

Historic skeletal populations (2,019 skulls)

The skulls of 1,012 Native American individuals were examined at the Smithsonian Institution (Washington, DC). The skulls comprising this sample were collected in Alaska, Arkansas, California, Illinois, Louisiana, Mississippi, New York, Ohio, Pennsylvania, South Dakota, and Virginia and date from the 16th–17th centuries AD. Postmortem basilar defects facilitated observation of the endocranium in many of these skulls.

Skulls of 204, 18th–20th century Negev, Israeli Bedouin adults (Lahav, Lahav "Z," Bir Sa'al, Wadi Qid, and Wadi Sulaf) were also examined, as well as 516 adult skulls from various archaeological sites (4th millennium BC–7th century AD) representing the historic populations of Israel.

Hungarian skulls of 287 individuals from the last few centuries (Fonyod, Helemba, and Ker-puszta) presently housed at the Hungarian Natural History Museum (Budapest) were also examined.

Cadaver studies (72 cadavers)

In addition to data from osteological collections, 72 dissected cadavers at the Hadassah Medical School (Hebrew University, Jerusalem, Israel) and the Sackler Faculty of Medicine (Tel Aviv University, Tel Aviv, Israel) were examined for macroscopic evidence of HFI. All of the individuals examined were of European origin. The average age of the female sample (n = 37) was 85.6 years, and for the males (n = 35), 84.0 years. Special attention was paid to vascular and cerebral spatial relationships with endostosis (i.e., a growth projecting inside the cranial cavity). Information about age, sex, number of live children (available for half of the sample only), and country of origin was taken from the medical records.

Macroscopic examination

Characteristics of hyperostosis frontalis interna. Previous, large-scale studies (e.g., Moore 1955) were based primarily on roentgenograms. In the current study on macroscopic recognition of HFI, the need for a new classification system was predicated. A classification method was therefore developed, based on the following morphologic criteria:

1) Extent of involvement (a, lesion diameter; b, lesion thickness; c, lesion size);

2) Appearance (a, isolated; b, continuous areas);
3) Border type (a, clearly demarcated; b, ill-defined);
4) Shape (a, round; b, lobular; c, elongated);
5) Location in frontal bone (a, anterior; b, posterior; c, orbital roof); and
6) Involvement of other bones (a, parietal; b, sphenoid; c, temporal).

Characteristics of hyperostosis cranialis diffusa. Females were also evaluated for hyperostosis cranialis diffusa (HCD). This was defined on the basis of three parameters: a) skull weight (as corrected for size by the use of the cranial module (length + breadth + height/3); b) cranial thickness measured at the midsagittal section, midpoint between bregma and lambda; and c) absence of evidence of nodularity or rugosity of the inner table. Normal values (thickness and size) were established for AA and EA females before normal ranges were determined. We also used the "border" values suggested by Perou (1964).

Microscopic examination

Unstained, decalcified, and nondecalcified sections of affected frontal bone were examined by light and polarizing microscopy. Scanning electron microscopy (SEM) was performed as follows: HFI samples were sectioned, cleaned, and affixed to an aluminum specimen mount. Specimens were then coated with 20 nm palladium/gold in an RMC-Eiko IB-3 Ion Coater (Tucson, AZ), and examined in a JOEL 840-A scanning electron microscope.

Radiography

Radiographic study, limited to 92 specimens from the Hamann-Todd Collection, was performed using a Hewlett Packard Faxitron Cabinet X-ray system (Corvallis, OR). Lateral radiographs were obtained of the full skull at 350 milliamp-sec, 75 Kvp. Radiographs of each hemicranium were separately obtained at 200 milliamp-sec, 65 Kvp. Radiographic observations were then divided into three categories: positive, negative, and inconclusive. Positive (+) meant that HFI was seen on X-ray of the intact skull. This was characterized as the widening of frontal bone, associated with irregularity of the endocranial surface. There was also variable increased density projecting below the endocranial surface. Negative (-) meant no identifiable changes on intact or hemicranium radiographs, and normal cranial thickness with "smooth" endocranial surface. Inconclusive (±) meant that minimal positive changes were identified on hemiskull radiographs only, or retrospectively on film of the intact skull.

CT scans were obtained for 22 representative skulls with HFI. These skulls were selected on the basis of characteristic variation, as delineated in Results (below).

The chi-square test was used to statistically evaluate differences among groups in regard to the HFI phenomenon.

RESULTS

Morphology

Macroscopic morphology characteristic of HFI. Using the morphologic characteristics outlined above, four types of HFI were recognized (Fig. 1). They have been listed in graduated order by magnitude of manifestation:

Type A (Fig. 2a,b): Isolated, elevated bony island(s), single or multiple, unilateral or bilateral, all of which exhibited discrete, often indented margins. These were generally under 10 mm in size, and were commonly found on the anteromedial part of the frontal bone.

Type B (Fig. 3): Nodular bony overgrowths, without discrete margins and with only slight elevation identified on less than 25% of the frontal bone. Occasionally isolated nodular areas were also identified.

Type C (Fig. 4): More extensive nodular bony overgrowth, associated with irregular thickening of up to 50% of the frontal endocranial surface. A tendency for greater elevation and coalescence was observed.

Type D (Fig. 5a,b): Continuous bony overgrowth, involving more than 50% of the frontal endocranial surface. The entire region was found to be irregularly elevated with sharp, clearly demarcated borders.

HFI was found to be quite varied in shape and size, ranging from small isolated endocranial elevations to extensive diffuse changes. The margins of individual foci were

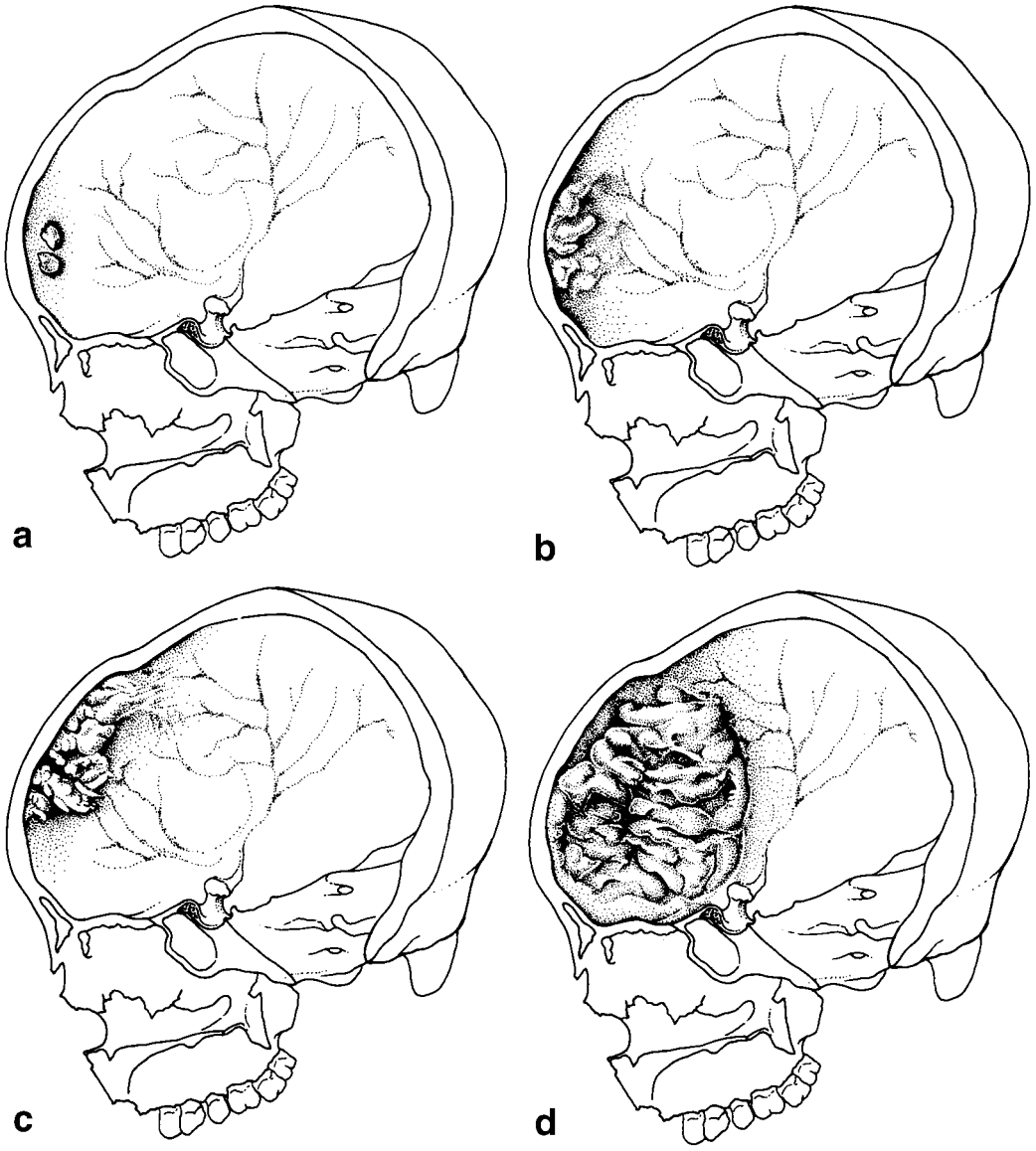
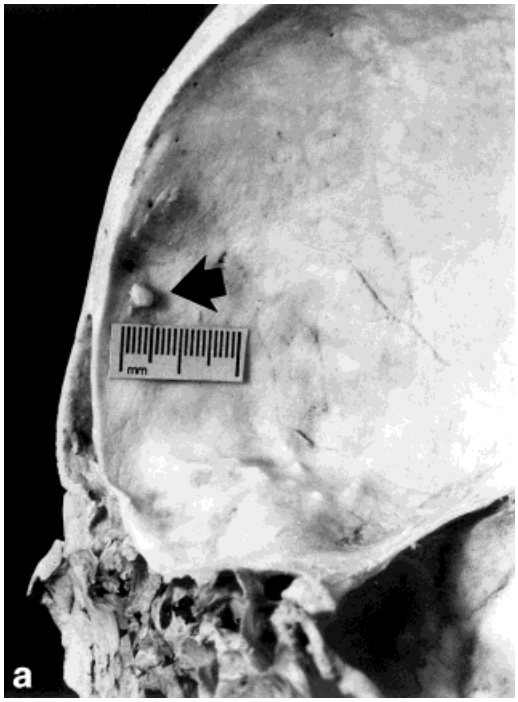


Fig. 1. Schematic presentation of HFI types A–D (see Figures 2, 3, 4, and 5).

on some occasions well-defined and on others difficult to distinguish (Fig. 2a). Often in the milder cases, frontal bone changes were limited to the anterior, parasagittal aspects. Intermediate stages were characterized by a loss of margination, precluding the identification of individual foci. This was associated with increased osseous thickening and the involvement of a greater proportion of the frontal bone. The most advanced cases were flattened, and "pancake-shaped" with sharp posterior margins (Fig. 5a,b). They exhibited clustered lobulations (Fig. 5a) or a cauliflower shape. Fine or shallow bony striations were noted. The degree of symmetry increased with the extent of involvement. Periosteal reaction was notably absent.

Hyperostosis cranii interna (HCI), which includes HFI, was the term used by Perou (1964) when the HFI process extended be-



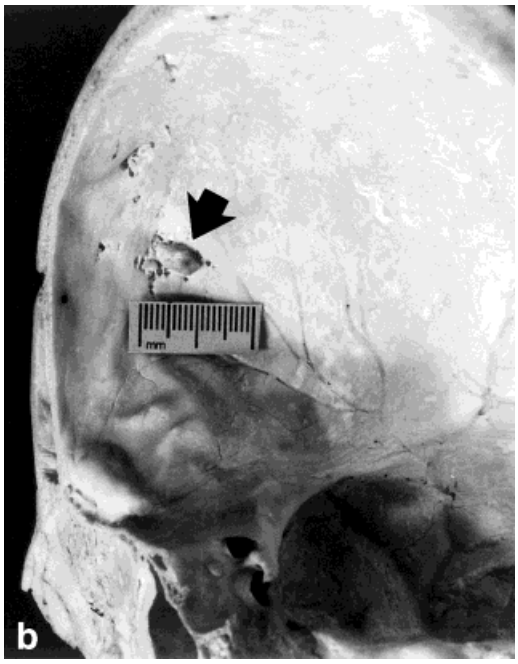


Fig. 2. HFI type A is characterized by isolated, elevated bony island(s), single (**a**) or multiple (**b**), unilateral or bilateral, all with discrete, often undermined margins (arrows). They are usually under 10 mm in size and are commonly found on the anteromedial part of the frontal bone.

Fig. 3. HFI type B is characterized by bony overgrowth(s) without discrete margins. Only slight elevation is noted (arrows).

yond the frontal bone to involve portions of either the parietal, temporal, and/or sphenoid bones (Fig. 6). This was found most commonly in association with extensive HFI frontal involvement. In the present study, classification type was advanced one level when HCI was identified.

In cases of HFI observed in the present study, bony formations of ridges and grooves were found to be aligned perpendicularly and obliquely to the midsagittal plane. These formations were funnel-shaped and tended to converge towards a focal point near the sinus. The grooves were occupied by large blood vessels, which drained into the superior sagittal sinus (Fig. 7a–d). Even the most severe cases of HFI did not cross suture lines. The skull midline and superior longitudinal sinus were consistently found to be free of HFI. The borders of the unaffected central region diverged as they extended posteriorly, reaching maximum separation at the bregmatic area (Fig. 5). Posteriorly, the ascending branch of the middle menin-

Fig. 4. HFI type C is characterized by more extensive nodular bony overgrowth (large arrows), associated with irregular thickening (small arrows) of up to 50% of the endocranial surface of the frontal bone. There is a tendency for greater elevation and coalescence.

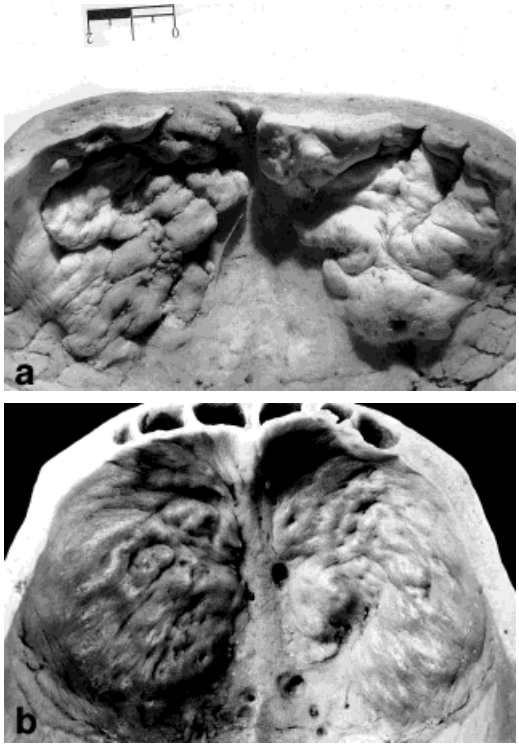


Fig. 5. HFI type D is characterized by continuous bony overgrowth, involving more than 50% of the frontal endocranial surface. The whole area is variably elevated (**a**) and usually manifests a sharp demarcation at its borders (**a**, **b**). The unaffected area along the midline flares out towards the bregmatic region. Scale bar in cm.

geal artery also served as a limiting factor, as HFI did not traverse this vessel. In the rare cases where parietal thickening was also present, the groove for the ascending branch of the middle meningeal artery was spared (Fig. 6).

The relationship between bone, dura matter, leptomeninges, blood vessels, and brain was examined in cadavers with HFI. In these cases, the space between the brain and the endocranial diploic plate appeared to be wider than in young individuals, leaving the brain suspended by blood vessels from the skull (Fig. 7a). The endosteal component of the dura, which was associated with the HFI, was very thin, fibrous in nature, and firmly attached to the bone (Fig. 8). In certain areas it seemed as if fibers from the dura were running under the bony ridges. It was observed that the meningeal dural layer of the frontal region adhered more firmly to its endosteal counterpart than it did in other regions of the endocranium (Fig. 8).

Microscopic (light and SEM) morphology characteristic of HFI. Upon histological examination, five distinctive osseous layers were revealed (Figs. 9a–c, 10). Layer A involved the ectocranial plate, consisting of normal dense lamellar bone with no evidence of bone remodeling or resorption. Layer B involved an apparently normal diploic space with trabeculae, associated cavities and no evidence of expansion. Layer C included a thin band of remodeled, disorganized, sclerotic lamellar bone, associated with small and large irregularly shaped cavities, with ill-defined margins. A widened zone of lamellar bone merged into the normal endocranial plate peripherally. Layer D involved a bulbous area consisting of numerous thin-walled blood vessels of varying diameter and large vascular sinuses, separated by thin bony septa (Figs. 10, 11). An

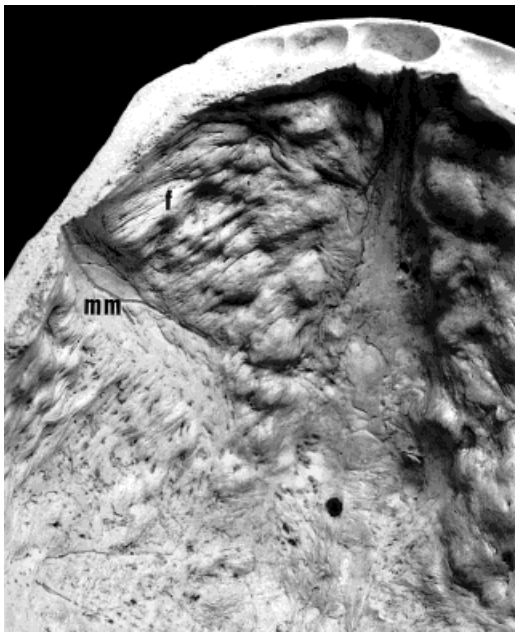


Fig. 6. Hyperostosis frontalis interna (HCI) with extension. Frontal bone manifests bony changes typical of HFI. Extension into the parietal bone is disrupted by the groove for the ascending branch of the middle meningeal artery. f, frontal bone; mm, middle meningeal artery.

irregular distribution of osteocytes and canals of varying diameters was also noted. Layer E involved a thin, concave shell of organized lamellar bone, traversed by blood vessels (Figs. 9, 10). In general, the morphology varied as one moved from the periphery (ectocranial plate) to the interior aspect of the skull.

Computerized tomography characteristic of HFI. Computerized tomography (CT) examination of 22 specimens confirmed the histological picture of HFI with five distinctive osseous layers (Fig. 11a–d). The most external layer, the ectocranial plate, remained of normal thickness, density, and organization. The diploic space, although slightly less dense in advanced cases of HFI, retained its normal volume, and was continuous with the diploic space in other parts of the skull. A hyperdense broad band with irregular margination was the next layer, as one moved internally. Then came the delicate hypodense bulbous region. The innermost layer was a very thin cortical residue, continuous with the endocranial plate.

Demographics

The distribution of the different types of HFI by sex, age, and ethnicity is delineated in Tables 2 and 3.

HFI in females. Twenty-four percent of the female sample manifested one of the four types of HFI. The frequency of HFI in EA females (26.5%) did not demonstrate a statistically significant difference from that of AA females (21.9%) ($\chi^2 = 1.957$, df = 3, $P = 0.581$). HFI seemed to be age-dependent in females, increasing from 11.8% in the youngest age group (20–29 years) to 44.2% in the oldest (aged 80 and over).

Magnitude of HFI manifestation in females. Magnitude of HFI manifestation also increased with age. Eighty-two percent of type A cases were under 50 years of age, while most cases of type D (87%) were found in individuals over age 50. No significant ethnic differences were observed in the overall distribution. Type A was slightly more common in AA females (3.5%) than in EA females (1.0%) ($\chi^2 = 4.464$, df = 3, $P = 0.215$). Type D, the most advanced, was similarly distributed among the two female groups (EA, 4.0%; AA, 4.7%).

A significant interaction existed between age and ethnicity. When the sample was divided into three major cohort groups (20–49 years, 50–69 years, and 70 years and over), and HFI types were combined in two categories (mild, types A and B; advanced, types C and D), HFI distribution among AA and EA females was significantly different ($\chi^2 = 53.25$, df = 11, $P < 0.001$). In EA females, the frequency of mild HFI increased with age: 9.4% in the youngest age group, 14.9% in the middle age group, and 20.9% in the old age group. Advanced HFI increased from 2.8% to 14.9% to 18.7%, respectively. In AA females, the frequencies of mild type (A and B) decreased with age: 13.8% in the young age group, 8.2% in the middle age group, and 7.1% in the old age

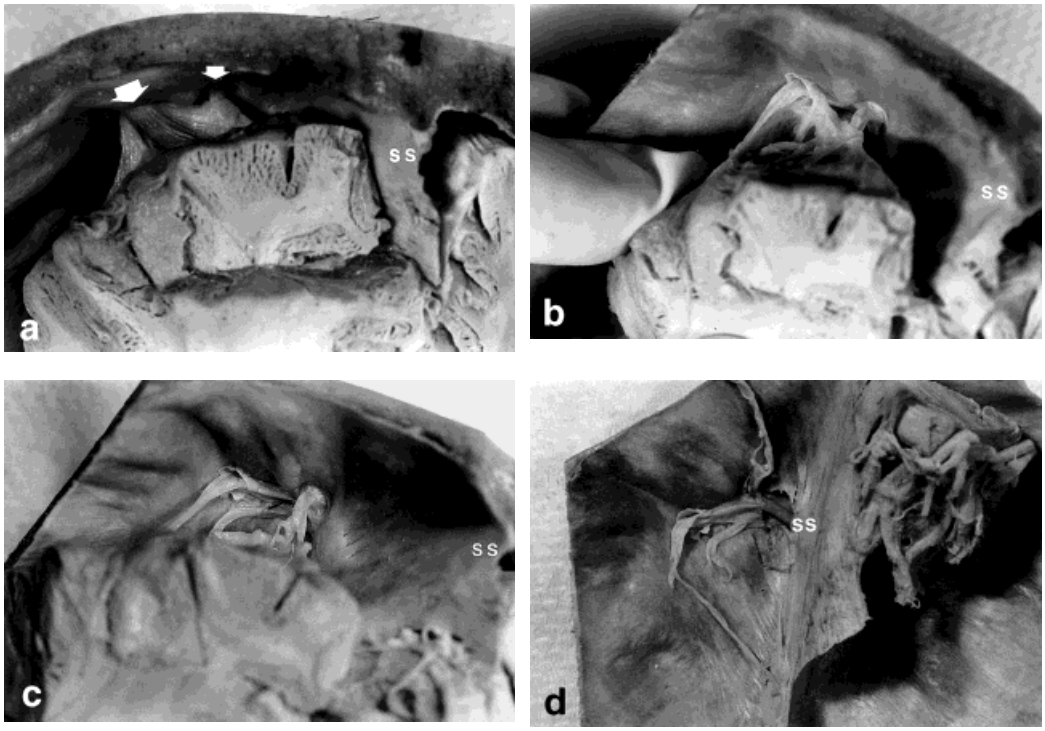


Fig. 7. Dissected specimen manifesting HFI. **a:** Superior cerebral veins (arrows), associated with leptomeninges enveloped by the HFI process, are clearly visible. **b:** Leptomeninges are partially removed, exposing cerebral veins. **c:** HFI topography coincides with cerebral vein orientation. **d:** Brain removed, with cerebral veins running perpendicular to and draining into the sagittal sinus. SS, sagittal sinus.

group. Advanced HFI (types C and D) rose from 2.8% to 19.4% to 28.6%, respectively.

Of further significance is the fact that while mild types (A and B) still predominated slightly over the advanced types (C and D) in the age 70+ cohort of EA females, in the AA cohort there were four times more cases of advanced HFI types (16 of 56 cases) than mild ones (4 of 56 cases) ($\chi^2 = 46.33$, df = 3, $P < 0.001$).

HFI in males. HFI was less common in males (Table 3) than in females, occurring in 5.2% of cases (i.e., 52 out of 1,007 cases). The frequency was similar in EA and AA males, at 4.7% and 5.8%, respectively ($\chi^2 = 0.559$, df = 3, $P = 0.906$).

A majority of cases were type A: 60% among EA males and 76% among AA males. In the AA male sample, most of the individuals with HFI type A were under 50 years of age (14 out of 19); in contrast, most of the EA males were over age 50 (13 of 16 skulls). HFI type B was noted in both populations, mainly among individuals over age 50. There was only one case of HFI type C in the male population, an EA individual in the age 60–69 cohort. Type D was not observed in the male skeletal population.

Radiological-anatomic correlation study

Results of the radiographic study are presented in Table 4. Successful identification of HFI radiographically was contingent upon the degree of osseous involvement. Positive identification was poor for HFI type A, at only 13.3% (Fig. 12). It increased to 44.1% in individuals with HFI type B. Almost all cases of types C and D (96.4%) were detected on radiograph.

An attempt to study HCD radiologically was unsuccessful. Neither intact nor hemicranial views rendered accurate recognition of HCD.

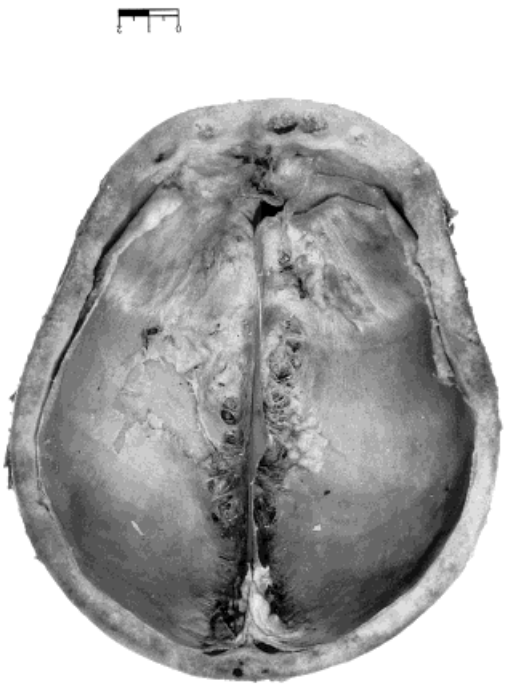


Fig. 8. Cadaver specimen. The part of the dura which covers the HFI is very thin and fibrous in nature, and is firmly attached to the bone. Scale bar in cm.

HFI in historic populations

None of the 1,012 Native American skulls, 204 Israeli Bedouin skulls, 516 historic skulls (4th millennium BC–7th century AD) from Israel, and 287 skulls from recent centuries in Hungary showed evidence of HFI. It is therefore clear that regardless of the geographical location of a population, HFI was a rarity in populations prior to the 19th century.

Cadaver studies

The distribution of HFI types in the cadaver sample appears in Table 5. The results supported our major findings in the skeletal populations, i.e., that although the phenomenon was found to be much more common and severe in females, it was also observed in males; that the relative magnitude of manifestation of the phenomenon did not increase after age 50; and that males rarely manifested HFI type D. The only male found with HFI type D had a single testis which, upon histological section, was found to be atrophied. The frequency of the HFI phenomenon in our century increased among older females (under age 80 years) by 7% (from 44.4% to 51.4%). In addition, the following observations were made. The average age of females with HFI was 86.2 years, and without HFI, 84.3 years. The average number of children was similar (0.71) among females with and without HFI. Seven out of the 14 females without HFI had children but were uniparous. All females with HFI who had given birth to children (5 out of 14) were multiparous. Of females with HFI, 64.3% had no children, compared to 50% in the group without HFI. The average number of children sired by the males was 1.4, for both HFI and non-HFI groups. The three males with HFI type B or beyond had no children.

Relationship between HFI and HCD

Among the 699 female skulls evaluated, 133 exhibited HFI only, 33 showed HCD only, and 34 demonstrated a combination of HCD and HFI. A total of 67 female skulls exhibited HCD, and 167, HFI (Tables 6, 7). The frequency of HCD skulls in the HFI sample (20.4%) was statistically higher than in the non-HFI group (5.6%) ($\chi^2 = 29.4$, df = 3, $P < 0.001$). Table 6 delineates the occurrence of HFI in combination with HCD and HCI. Of the 167 HFI cases, 19.2% presented extension to other cranial bones (HCI). This was strongly associated with HFI types C and D (Table 6). Simultaneous occurrences of HFI, HCI, and HCD were relatively rare (4.2%).

HCD distribution by age, with and without HFI, is presented in Table 7. Of the 33 individuals with HCD, 76% were under 40 years of age. The other 8 skulls were from the 40–50-year-old cohort. No individual with HCD alone was over 50 years of age. On the other hand, HFI + HCD in combination did not show an age-biased distribution.

The coexistence of HFI and HCD was not related to the extent of the HFI phenomenon. Of skulls with HCD, 17.6% were associated with HFI type A, and 19.5% were associated with HFI type D (Table 6).

Is the coexistence of HFI and HCD associated with ethnic origin? While there were no statistically significant differences in data associating HFI and HCD frequencies in EA

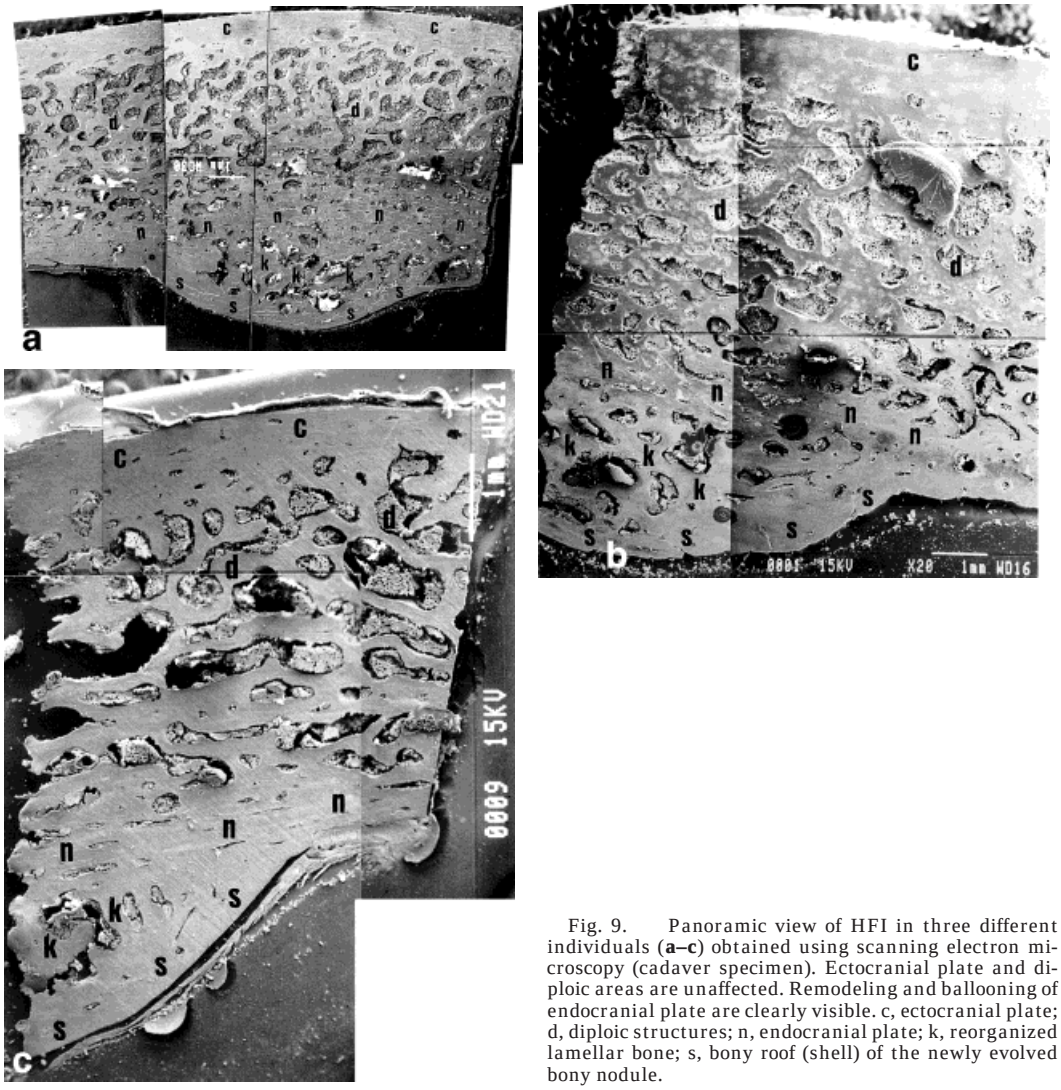


Fig. 9. Panoramic view of HFI in three different individuals (**a–c**) obtained using scanning electron microscopy (cadaver specimen). Ectocranial plate and diploic areas are unaffected. Remodeling and ballooning of endocranial plate are clearly visible. c, ectocranial plate; d, diploic structures; n, endocranial plate; k, reorganized lamellar bone; s, bony roof (shell) of the newly evolved bony nodule.

and AA females (Table 8), the frequency of HCD was significantly higher in AA females, 14.7% (59 out of 401 cases) vs. 2.7% (8 out of 298) ($\chi^2 = 28.63$, df = 3, $P < 0.001$). In the EA group, only 6 females (2.0%) manifested a combination of HCD and HFI, while in the AA group, 28 females (7.0%) demonstrated both phenomena ($\chi^2 = 9.13$, df = 3, $P = 0.027$). HCD alone was found in only 2 (0.6%) EA females as contrasted with 31 (7.7%) AA females ($\chi^2 = 19.02$, df = 3, $P < 0.001$). The 2 EA females were found in the age 40–49 cohort, while 25 of the 31 AA females with HCD alone were under age 40.

DISCUSSION

Definition and differential diagnosis of HFI?

The diverse terminology related to the phenomenon of endocranial bone thickening (e.g., Stewart-Morel syndrome; Morgagni-Morel syndrome; metabolic craniopathy; endostosis cranii; enostosis cranii; endocraniosis) testifies to the diversity of opinion concerning the nature of this condition (Perou, 1964; Moore, 1955; Calame, 1951; Henschen, 1949). Perou (1964) found the terminology of Moore (1955) (HFI) to be misleading, and offered the broader term

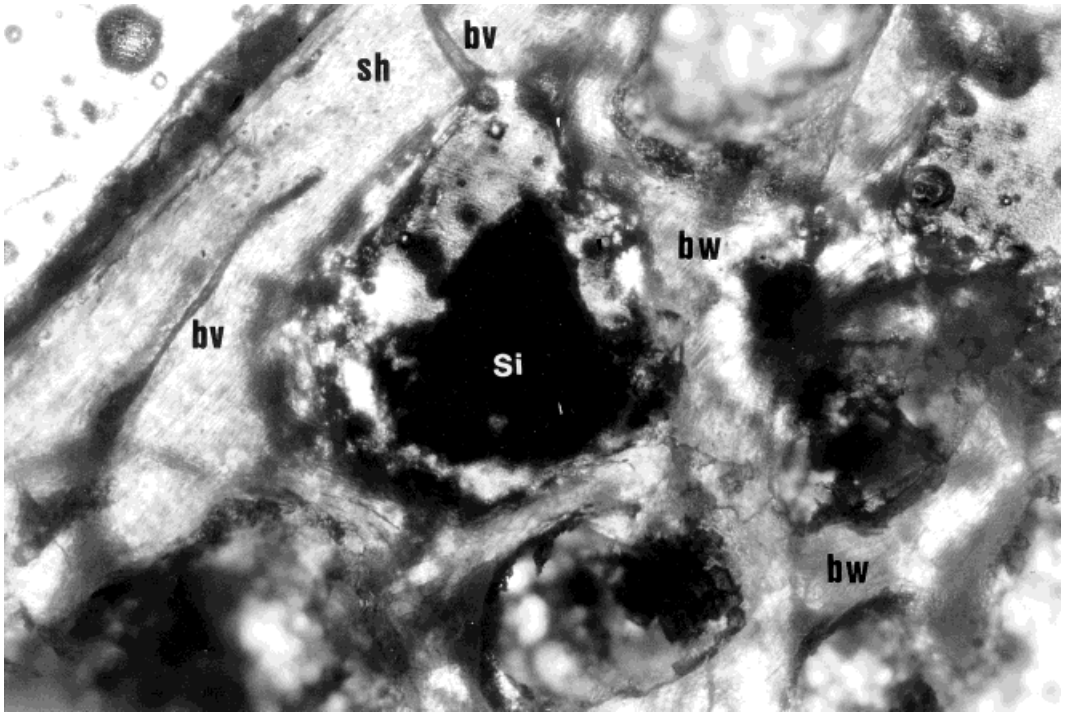


Fig. 10. Histological section through a bony nodule in HFI. Notice that the shell (sh) is composed of normal, organized lamellar bone, and is traversed by blood vessels (bv). The large cavities, probably vascular sinuses (si) which comprise the ballooning area, are irregular in shape, and separated from each other by bony walls (bw) made of disorganized lamellar bone.

HCI (hyperostosis calvaria interna) in its place. The term HCI combined all cases of endostosis, regardless of their endocranial location. In the present study we selected the term HFI instead of HCI for two main reasons: 1) HFI is the common term in the medical literature, and 2) when other areas of the endocranium are involved the etiology may be different. An example is the case of an extremely obese male who died at 30 years of age with advanced enostosis in the occipital region (Fig. 13).

The differential diagnosis of HFI includes focal masses (e.g., meningioma, endosteal osteoma), subdural and dural calcification, and diffuse skull processes (Resnick and Niwayama, 1988) such as Paget's disease, acromegaly, and fibrous dysplasia. The characteristics of HFI (including clear boundaries along the middle meningeal artery, unaffected midline, and a tendency towards bilaterality) allow a clear differentiation from most of the aforementioned processes. Distinguishing the earliest stage of HFI (type A) from a solitary small bony mass such as an endosteal osteoma is difficult. Osteomas tend to be solid ectocranial processes (Resnick and Niwayama, 1988), and are rarely bilateral. Large bony masses such as meningiomas and calcified subdural hematomas do not follow the criteria for HFI as defined in this paper. Acromegaly is a generalized process with an increase in the diploic space and significant thickening of ecto- and endocranial tables of all skull components. Fibrous dysplasia is a process of diploic space expansion, associated with the thinning of both ectocranial and endocranial tables. Paget's disease involves most of the cranial bones, and shows coarsening of bone trabeculae and thickening of both endo- and ectocranial plates. Facial bone involvement is common in many of the above-mentioned disorders, but has not been recognized in HFI.

How is HFI formed?

Perou (1964) defined HCI (which includes HFI) as a "bilateral, dysplastic, slow, often

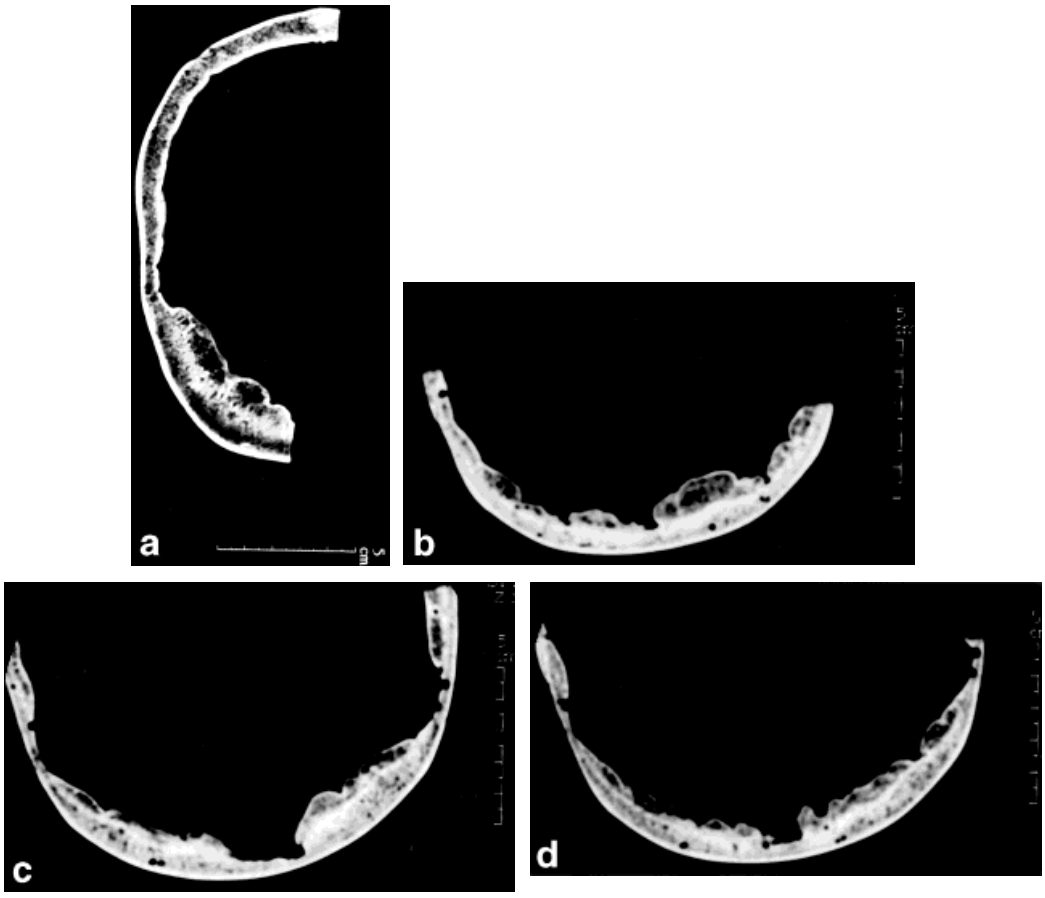


Fig. 11. CT scans of advanced HFI (stage D) in three different individuals (**a–d**). Note that while ectocranial plate and diploic space retain their normal appearance in the region of the nodule, the normal endocranial plate is not seen. In its place, three different areas are identified: a hyperdense layer, a ballooned, vascularized area, and a thin cortical shell encapsulating it.

TABLE 2. Distribution of HFI types in females, by age and ethnic origin[1]

Age (years)	European American HFI types				African American HFI types				Total
	A	B	C	D	A	B	C	D	
20–29	0	1	0	0	5	5	1	0	12
30–39	1	2	0	0	3	5	0	0	11
40–49	0	6	3	0	5	11	2	4	31
50–59	1	6	3	2	1	4	3	2	22
60–69	0	8	7	3	0	3	11	3	35
70–79	0	13	8	4	0	2	4	3	34
80+	1	5	2	3	0	2	2	7	22
Total	3	41	23	12	14	32	23	19	167
Total		298				401			699

[1] HFI, hyperostosis frontalis interna.

TABLE 3. Distribution of HFI types in males by age and ethnic origin[1]

Age (years)	European Americans HFI types				African American HFI types				Total
	A	B	C	D	A	B	C	D	
20–29	0	0	0	0	3	0	0	0	3
30–39	1	2	0	0	5	0	0	0	8
40–49	2	0	0	0	6	1	0	0	9
50–59	5	1	0	0	3	1	0	0	10
60–69	5	4	1	0	2	1	0	0	13
70–70	1	3	0	0	0	2	0	0	6
80+	2	0	0	0	0	1	0	0	3
Total	16	10	1	0	19	6	0	0	52
Total		573				434			1,007

[1] HFI, hyperostosis frontalis interna.

self-limited and benign, occasionally progressive and aggressive, proliferation of bone involving primarily the inner table of the skull, with or without participation of the diploe, and with a predilection for the frontal squama" (pp. 54, 64). According to the present study, HFI should be defined as follows: "a disorder of the endocranial plate

TABLE 4. Accuracy of radiological identification of HFI by type in 92 specimens[1]

	Females				Males			
Type[2]	+	−	±	Total	+	−	±	Total
A	1	8	2	11	2	14	3	19
B	12	7	4	23	3	5	3	11
C	13	0	1	14	1	0	0	1
D	13	0	0	13	0	0	0	0
Total	39	15	7	61	6	19	6	31

[1] HFI, hyperostosis frontalis interna. +, positive identification; −, HFI not seen; ±, inconclusive for HFI.
[2] For HFI type description, see text.

Fig. 12. HFI type A, seen on oblique radiograph. The two circular shadows of uniform density (arrows) represent small cranial nodules. On routine lateral X-ray, the two nodules would not be observed due to superimpositioning.

TABLE 5. Distribution of HFI types in cadaver population[1]

HFI types[2]	Female	Male	Total
A	7 (18.9%)	4 (11.4%)	11 (15.3%)
B	3 (8.1%)	1 (2.8%)	4 (5.5%)
C	6 (16.2%)	1 (2.8%)	7 (9.7%)
D	3 (8.1%)	1 (2.8%)	4 (5.5%)
No HFI	18 (48.6%)	28 (80%)	46 (63.9%)
Total	37 (100%)	35 (100%)	72 (100%)

[1] HFI, hyperostosis frontalis interna.
[2] For HFI type description, see text.

which remodels into a more cancellous phenotype." This phenomenon appears to spare both the ectocranial plate and the diploic space. The decision as to which definition is more appropriate depends on our understanding of the development of HFI.

TABLE 6. Frequency of hyperostosis frontalis interna (HFI) in association with hyperostosis cranialis diffusa (HCD) and hyperostosis cranii interna (HCI), with African American females and European American females combined

Type[1]	HFI	HCD + HFI	HFI + HCI	HCD + HFI + HCI
A	17	3 (17.6%)	0	0
B	73	15 (20.5%)	1	0
C	46	8 (17.4%)	12	2
D	31	8 (19.5%)	20	5
Total	167	34 (20.4%)	33 (19.7%)	7 (4.2%)

[1] For HFI types, see text.

TABLE 7. Distribution of HCD skulls, by age, in two skull populations: with HFI (n = 167) and without HFI (n = 532)[1]

Age	HFI + HCD (34 out of 167 HFI skulls)					HCD
(years)	Type A	Type B	Type C	Type D	Total	only
20–29	1	0	0	0	1	17
30–39	0	4	0	0	4	8
40–49	2	7	1	2	12	7
50–59	0	0	3	0	3	1
60–69	0	2	2	3	7	0
70–79	0	2	1	1	4	0
80+	0	0	1	2	3	0
Total	3	15	8	8	34	33

[1] HCD, hyperostosis cranialis diffusa; HFI, hyperostosis frontalis interna.

TABLE 8. Frequency of HFI and HCD and the combination of the two in the female groups[1]

	European American (n = 298)	African American (n = 401)
HFI		
Total cases	79 (26.5%)	88 (21.9%)
HFI only	73 (24.5%)	60 (15.0%)
HFI + HCD	6 (2.0%)	28 (7.0%)
HCD		
Total cases	8 (2.7%)	59 (14.7%)
HCD only	2 (0.7%)	31 (7.7%)

[1] HFI, hyperostosis frontalis interna; HCD, hyperostosis cranialis diffusa.

Despite vast histological studies of HFI (e.g., Perou, 1964; Thevoz, 1966), there is much disagreement among researchers. Perou (1964) stated, "The words growth and deposition are both used because one cannot be sure, as yet, whether the newly formed bone grows from the inner table or is deposited on it" (p. 69). Later, he claimed that both processes were involved. Our histological observations indicate that the types of HFI represent sequential stages of a single process. This process can stop at any stage and

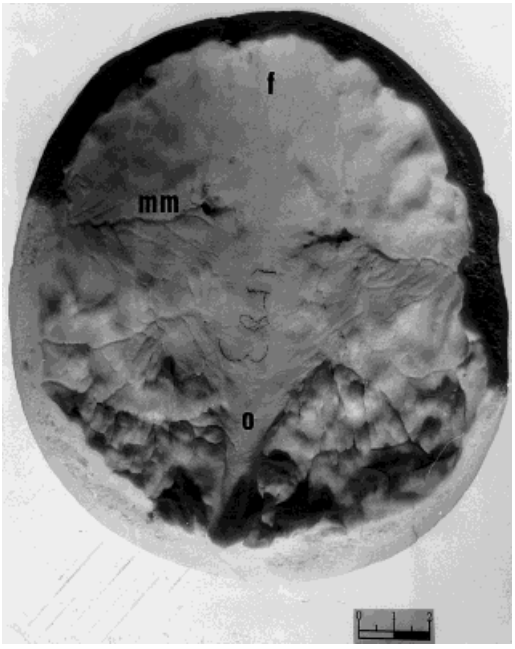


Fig. 13. Endocranial changes in an extremely obese young 30-year-old male. Note the dramatic changes in the occipital region. f, frontal bone; mm, middle meningeal artery; o, occipital bone. Scale bar in cm.

become stable, or retreat and disappear over time, or continue to grow.

Figure 14 presents three models to explain HFI: the "American model" (A); the global model (B); and the European model (C). The American model, proposed by Moore (1955), describes HFI as a process that triggers proliferation of spongy bone, increasing diploic volume by pushing the inner table internally. The outer table is not affected due to its greater thickness and durability. The European model (C), proposed by Thevoz (1966), presents HFI as a process which transpires exclusively in the dura, and is triggered by enlargement of the intradural vasculature. The global model (B), proposed by the present research team, was deemed "global" because of the varied nationalities of the contributors.

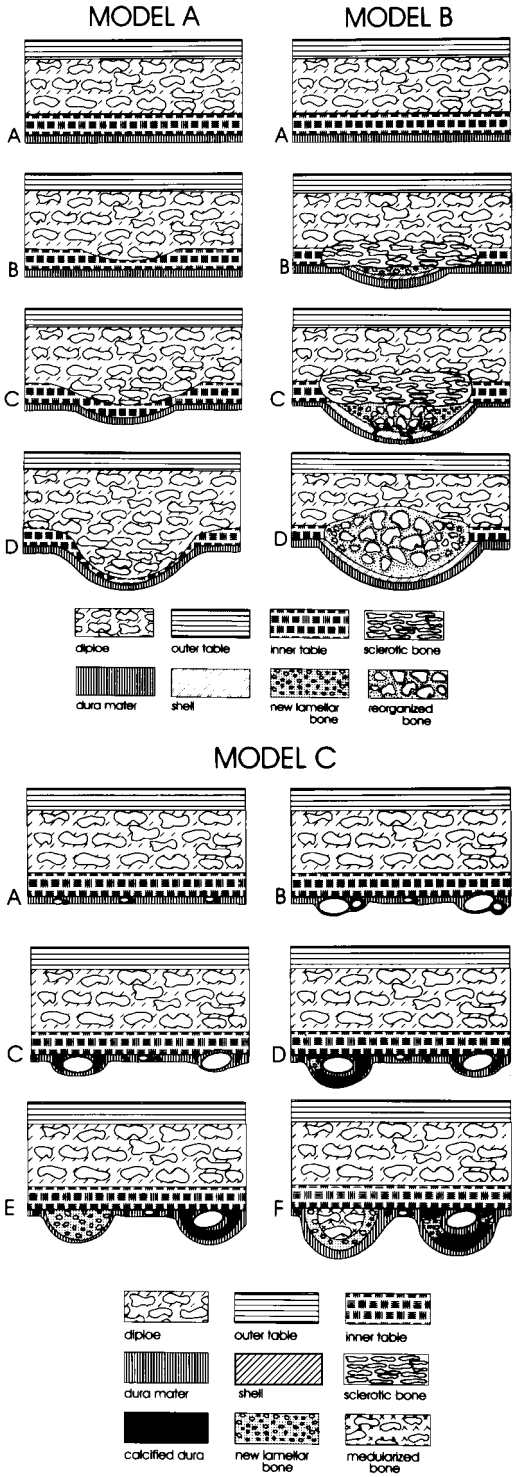


Fig. 14. Three models explaining the HFI phenomenon: the "American" (model A), the "global" (model B), and the "European" (model C). Model B is suggested by the present authors. **A–D** and **A–F** represent the stages of HFI.

The global model proposes a four-stage process which begins when osteogenic cells cause a disorganized diploization process in the inner table (stage A). These changes trigger the superimposition of newly formed lamellae on the inner table by the periosteum (stage B). The early compact hyperostosis is composed mainly of new lamellar bony layers deposited by the dura. In stage C, numerous blood vessels penetrate the lamellar bone from the dura, inducing bone proliferation. Over time, the original inner table becomes sclerotic and the newly formed bone undergoes dramatic reorganization with numerous large and irregular cavities (apparently blood sinuses). In this stage, Haversian systems may also be seen. These enlarged cavities support the raised endocranial plate ,which is recognized macroscopically as the remodeled overgrowth called HFI. In the final stage (stage D), the inner plate totally disappears, the reorganized bone expands towards the diploic space and the cranial cavity. In stage D only, a thin shell of lamellar bone remains to envelopes the bulbous cavity.

The rugose topography of HFI is probably due to multiple focal areas of subdural ossification causing regional variation in dural activation. According to our model, neither the external plate nor the diploe are directly involved. We therefore contest the statement of Perou (1964) that "the diploe is primarily affected and pushes the inner table downward" (p. 72). We further disagree with the proposition that dura mater does not participate in the hyperostotic process (Perou, 1964, p. 72). The bulging of the inner plate is primarily due to newly formed lamellar bone produced by the endosteal dura. Based on our model, there appears to be no basis for assigning names to different types of HFI, such as senile hyperostosis or hyperostosis cranii syndrome. We believe these to be different stages of the same process.

Is HFI a purely female phenomenon?

HFI is much more common in women than men. In the present sample it occurred in 23.9% of females and in 5.2% of males. Radiological studies on the general population such as that of Marlet (1974) reported similar numbers (20% for females and 2% for males). In the elderly group (over 60 years of age), the ratio was less dramatic: 51.4% vs. 20% in the cadaver sample and 38.7% vs. 7.7% in the skeletal sample. In a roentgen study, Gershon-Cohen et al. (1955) reported HFI in 62% of evaluated females over 60 years of age, and 0% in males of the same age cohort. In the present study, 67.3% of affected males manifested only mild HFI (type A), which was the least common among females (10.4%). In the skeletal sample, only a single male exhibited HFI type C, and none exhibited HFI type D. Among the cadavers studied, the single male who manifested HFI type D also exhibited a single atrophied testis. The main reasons for the high sex ratio (ca. 10:1) in the literature (e.g., Moore, 1955; Marlet, 1974) are that 1) many were X-ray-based studies and hence overlooked many males with type A HFI; and 2) in many studies, ethnic and age factors were ignored. The ratio of 5:1 in the age cohort under 60 years and 3:1 in the age cohort over 60 years may be more reflective of the actual situation.

Considering the different frequencies and magnitudes of manifestation of HFI in males and females, doubt could be cast as to whether they are the same phenomenon. Data from anatomical examination, histological sections, and CT scans indicate that the same process underlies the bony metamorphosis in both sexes. The discrepancy in frequency and magnitude of manifestation may simply represent differential susceptibility to the causative factors.

Is HFI a progressive phenomenon and is it age-related?

The increase in the relative number of individuals with types C and D, and the decrease in cases with types A and B with age, suggest a progressive age related phenomenon. The aging relationship is more pronounced in females than in males and clearer in AA females than in EA females. Changes in the frontal bone can appear very early in adult life and apparently develop and progress at a varying rate throughout life. Analysis of past literature is compromised, for researchers have generally combined the questions of progression and age. Moore (1955) and Knies and Lefever (1941)

maintained that HFI progressed with advancing age, while Pederson (1947), Salmi et al. (1962), and Marlet (1974) claimed HFI not to be a typical aging phenomenon. While they noted an increase in the frequency of HFI in women over age 50, they claimed that the magnitude of manifestation of HFI did not correlate well with age. Marlet (1974) maintained that HFI can develop during an 8-year period and then remain dormant for the next 6–11 years. Anatomical studies, which are cross-sectional in nature, cannot directly evaluate these hypotheses, but they can provide a general time scale for HFI. The mildest form of HFI (type A) can appear as early as the twenty-first year, while advanced HFI (type D) does not appear before age 40. Nevertheless, the fact that the female cadaver sample showed a different HFI aging pattern from the female skeletal sample of corresponding age and that AA and EA females also differed in HFI aging pattern, testifies to the complex nature of HFI and to the fact that age is not an independent factor but rather interacts with ethnicity and chronology.

From our histological analysis it seems that HFI has a "self-limiting" mechanism. This is indirectly supported by the fact that among cadaver cases where all females were over age 70 years, the frequency of HFI type B and HFI type D was the same (8.1%), while type C was twice as frequent (16.2%). Marlet (1974) claimed that "HFI is an irregular process which once started, can show progression but can stabilize or even subside" (p. 473). Based on their radiological study, Salmi et al. (1962) proposed that HFI reaches its peak from age 40–60, and then rapidly diminishes. All this contrasts with the hypothesis that HFI is a process which reaches its maximum at an advanced age. The disagreement between studies may be related to the fact that many past studies were based on biased samples which compromised their conclusions. For example, in Marlet (1974), the age cohort 80–85 was represented by 3 individuals and the age cohort 40–49 by 60. The jump in HFI frequency among females at age 50, as reported by Pedersen (1947) and Marlet (1974), has a similar bias, and was contradicted by the current study. Similarly, the conclusion that HFI is not a typical aging phenomenon (Salmi et al., 1962) is also problematic. Indeed, in the present series there was a gradual increase in HFI frequency among females: 10.1%, 20–40 years of age; 22.4%, 40–60 years of age, and 38.7%, over 60 years of age (Table 2). In a study of 700 skeletons, Henschen (1949) reported that 91% of the severe cases of HFI and 83% of the mild cases (type A) were over 60 years of age.

HFI appears to be an age-related progressive phenomenon. Although the regression of HFI is conceivable, the relative magnitude of manifestation of HFI cannot be used as supporting evidence. A prospective longitudinal study of at least 5 years is needed to answer this question. Anatomic study has the obvious limitation of cross-sectional visualization.

A longitudinal study would also allow follow-up to determine if this is a truly progressive process. These questions can be pursued by review of CT studies on individuals with HFI who have been serially evaluated. Changes over time and the impact of other clinical variables could then be tested.

What is the relationship between HCD and HFI?

This is one of the key unsolved questions in understanding HFI. Moore (1955) considered HFI and HCD to be different manifestations of the same process, with HFI as a precursor to HCD. Henschen (1949) believed them to be totally different processes. Perou (1964) did not consider HCD a condition per se but instead, the end result of several different unrelated pathological processes. He stressed that idiopathic HCD should not be confused with HCI, since HCD is primarily a dystrophic or degenerative process not related to heredity, not influenced by sex or age, without racial predominance or endocrine imbalance, and with no specific clinical picture. He recognized the fact that both processes may coexist, especially in the most advanced cases of HCI, but could not explain the association.

Marlet (1974) reported that 20% of hyperostotic female skulls also demonstrated HFI and that HCD was four times greater in females than males. Many authors (Marlet, 1974; Pedersen, 1947; Perou, 1964) believed

that this diffuse calvarial hyperostosis tends to stabilize with age. According to the present study, 19.0% of 699 female skulls showed signs of HFI only, 4.7% HCD only, and 4.9% both HFI and HCD. Of the 167 skulls with HFI, 34 also had HCD (20.4%). Of the remaining 532 skulls without HFI, 33 had HCD only (5.6%). Of the 67 skulls with HCD, 50.7% also had HFI. Although the occurrence of HCD with HFI was independent of the magnitude of manifestation of HFI, the question arose as to whether the coexistence of HFI and HCD is coincidental.

To try to answer this question, five aspects of the relationship between HFI, HCI, and HCD were considered. 1) HCI refers to the occurrence of HFI in combination with hyperostosis of other cranial bones (Table 6). This was present in 19.7% of the 167 cases and was strongly associated with advanced HFI types. The combination of all three phenomena, HFI, HCI, and HCD, was rare (4.2%). 2) The combination of HFI and HCD is clearly age-independent (Table 7), while each of the components (HCD, HFI) is age-dependent. 3) HCD becomes rare after age 50, while HFI becomes more frequent after that age. 4) The magnitude of manifestation of HFI does not correlate with HCD, and vise versa. 5) There is a strong racial factor to HCD. Most HCD cases were reported from young AA and EA females. It therefore seems incorrect to assert that HCD cases will develop some degree of HFI if they live long enough. On the other hand, it is possible that HCD begins early in life, reaches its peak in early adulthood, and then gradually resorbs. Individuals who also manifest HFI, however, do not follow this pattern. Whether the process that produces HFI retards bone resorption in females after menopause would be an interesting question for future study.

Since AA females manifest a greater overall bone mass than EA females (e.g., Chon et al., 1977; Seale, 1959), it is not surprising to find more HCD cases among AA females. In addition, a much lower rate of bone formation is noted in AA than in EA (Weinstein and Bell, 1988). This lower rate of bone formation and resultant bone remodeling could be a further factor in the differential racial changes in HFI, as well as the marked increase in HCD in AA females.

To summarize, the overlap between HFI and HCD cannot be explained in accordance with age or magnitude of manifestation. Most of the overlap between HFI and HCD is found in the AA female group, which presented with onset of HCD at an earlier age. HCD, which is strongly linked with the ethnic factor, is positively correlated with bone thickness while HFI is not. This clearly testifies to different etiologies for HFI and HCD.

Validity of roentgenograms in HFI studies

A large discrepancy exists between the actual incidence of HFI as determined by macroscopic study, and that recognizable on routine clinical X-ray. The latter is asserted with the assumption that a lateral view X-ray of the complete defleshed skull reflects what would be seen in the living individual. In the intact skull, the superimposition of structures limits visualization, and can transform irregular nodular overgrowth seen on hemiskull radiographs into a smooth continuous shadow. Pathologies such as meningioma and posttraumatic subdural and dural calcification may cause diagnostic confusion. Classification of HFI into types A–D cannot be reliably pursued by routine X-ray examination. Type A is rarely and type B infrequently detected on routine X-ray. Similarly, the various forms of HCI are not recognizable on routine X-ray.

The radiological-macroscopic correlation relates to two major misconceptions: 1) that HFI is an old-age phenomenon, and 2) that a high female:male ratio (10:1) exists. Although HFI types A and B appear in young women, these are the dominant types in the male population of all ages. The inability to identify most cases of HFI types A and B on routine X-ray distorts the sex ratio estimation. While radiographs can contribute significantly to the understanding of disease (Resnick and Niwayama, 1988), we agree with Anton (1997), that they have limited value for the study of the full HFI spectrum. Barber et al. (1997), based on radiological criteria only, claimed to detect HFI in 31% of the females from St. Peter's Church Cemetery, Barton-on-Humber, UK (12th–18th century). This extremely high rate, in part, is probably due to the fact that any endos-

teal new bone on the inner table, according to their method, would be HFI. Since no data were presented for a modern control sample, it is hard to appreciate the validity of their results.

HCD cannot be recognized on radiographs, as the degree of bone density appears to be the main determinate, rather than a thickness measurement.

Is HFI a modern phenomenon?

HFI was present in 25% of women and 5% of men in the general population of the early 20th century. Although some studies (e.g., Barber et al., 1997) claimed a similar rate for archaeological populations, most studies emphasize the dearth of HFI in historic populations (e.g., Anton, 1997; Watrous et al., 1993; Stroud and Kemp, 1993; Anderson, 1993; Armelagos and Chrisman, 1988; and the present study, reporting its absence in 2,019 adult skulls of historic populations from different parts of the world). The key question, then, is: why was HFI apparently so rare in historic populations as compared to present ones? One logical answer would be that changes in demography, particularly longevity, have caused this change (e.g., Armelagos and Chrisman, 1988). Our results, as well as those of Moore (1955) and others, suggest that HFI would be identified in historic populations (given the sample size examined), if it had today's prevalence. In the present series of modern skulls, 16.4% of females with HFI were under 60 years of age, and 7% under age 40. If HFI were present in archaeological populations we would expect to find it in at least 7% of the females. While it is possible that investigators did not recognize HFI types A and B and thus did not report it, HFI was not identified in the 2,019 adult skulls analyzed here. The change in prevalence therefore appears to be real. Table 9 tells us that females already born in the early 19th century were likely to manifest HFI in their postmenopause life. This led us to think that the "turning point" for HFI frequency in Western societies was the "industrial revolution" (ca. 1760), which had great impact on female lifestyle and longevity.

The reported incidence of HFI in modern 20th century populations is subject to much disagreement (Arensburg, 1989; Marlet, 1974; Hawkins and Martin, 1965; Salmi et al., 1962; Moore, 1955; Gershon-Cohen et al., 1955; Calame, 1951; Henschen, 1949; Oldberg, 1945; Eldridge and Holm, 1940; Morel, 1930). The discrepancy is derived from four main factors: 1) the method used (X-ray vs. skeletal analysis); 2) the definition of HFI (extent or thickness/solitary areas); 3) sample differences (size, ethnic origin, age, and sex distribution); and 4) the temporal discrepancy (early vs. late 20th century). Nevertheless, a summation of the data from 20th century populations clearly shows two trends: 1) an increase in the percentage of HFI during the last century among females, and 2) the constant level or slight increase among males. One possible explanation for the dearth of HFI in historic populations is discussed below.

TABLE 9. Frequency of HFI in female group, by year of birth

Year of birth	All	HFI	A	B	C	D	%
1835–1840	4	3	1			2	75
1841–1845	9	3		1	2		33
1846–1850	12	6		4	2		50
1851–1855	23	12		4	5	3	52
1856–1860	24	9		2	5	2	37
1861–1865	24	8		5	2	1	33
1866–1870	25	7		3	1	3	28
1871–1875	35	12		9	3		34
1876–1880	43	12	1	7	3	1	28
1881–1885	58	6		2	2	2	10
1866–1890	47	4		2	1	1	8
1891–1895	58	14	5	8	1		24
1896–1900	45	5	1	1	3		11
1901–1905	35	5	2	3			14
1906–1910	27	2	1	1			7
1911–1915	8	1		1			12
Total	477	109	11	53	30	15	

Why the frontal bone?

While progress has been made in the understanding of possible factors behind HFI, its presentation in the frontal bone remains a mystery. As previously mentioned for hitherto unknown reasons, the frontal bone is a favored hormone target. One clue might lie in the fact that the HFI process almost always begins in the middle one third of the frontal squama. Morel (1930) suggested that the point of origin corresponds with the original centers of ossification of the bone. Calame (1951), on the other hand, objected to this proposition. We know

that during adulthood, these centers remain active bilaterally. Estrogen stimulus may reactivate the primary centers of ossification of the frontal bone, causing abnormal bone growth. The bilaterality of HFI, and the fact that the hyperostosis is limited to areas associated with the ossification centers and excludes both the midline area (metopic suture) and bregmatic area (anterior fontanel), lend further support to the notion of primary ossification center involvement. The frontal bone may predominate due to its special vascularization. Perou (1964) mentioned that HFI is frequently observed in proximity to a depression which may contain vascular openings. Analysis of the vascular territories in the calvarium demonstrates that both soft and hard tissues in the frontal region form a separate angiosome (a composite block of tissue supplied by a named source artery). The diploic venous system of the frontal bone is independent of those (parietal and occipital) draining other calvarial bones, and the grooves between the bony ridges of HFI are occupied by veins exiting the diploe. Another unique aspect of the frontal bone is the adherence of the dura to its inner surface.

What are the morphogenesis and etiology of HFI?

In his extensive monograph on cranial hyperostosis, Perou (1964) stated that HCI "needs a given soil to start and a given stimulus to manifest itself" (p. 83). He suggested endocrine imbalance, due either to congenital inadequacy or deterioration due to advancing age, as the primary mechanism. The notion that female hormonal changes were responsible for HFI was first put forth by Richter (1939). He claimed that the process disappeared with the passing of the endocrine imbalance of menopause. The present study, as well as those of Calame (1951) and Morel (1930), suggest dysendocrinism to be the most plausible cause. We believe that functional disturbance of the gonads, i.e., faulty estrogen stimulation of or abnormal progesterone effect on the ovaries, or inadequate androgen stimulation by the testis, are the main causes of HFI. Morel (1930) and Calame (1951) suggested a disturbance of the tubero-infundibular portion of the pituitary gland as an etiologic factor of hyperostosis frontalis interna. Calame (1951) claimed the symptoms of HFI to be the same as those of infundibulo-pituitary disturbance (e.g., adiposity, genital dystrophy, disturbance of sugar metabolism). He placed particular emphasis on gonadal factors and noted that male patients with HFI were commonly feminized, with atrophic testes. Perou (1964) found no evidence of feminization among males with HFI, but stressed that 5 out of 6 HFI cases among males presented testicular underdevelopment or atrophy. Likewise, data from the present study support the notion of a relationship between HFI and male gonadal imbalance or insufficiency. We suggest that instead of asking whether the relative preponderance of female HFI is a clue to its etiology, the question posed should address whether the low frequency and intensity of HFI among males are clues to its etiology. The latter question received an affirmative response in the present study. Males probably developed HFI type D under extreme conditions of hormonal imbalance such as atrophied testes.

We believe that birds and breast cancer supply crucial clues to the etiology of HFI. Several species of birds regularly demonstrate bony changes in the frontal bone known as "aviforme hyperostosis" (Schmitt, 1974). Moreover, estrogen plays an important role in the endocrine homeostasis of birds (Gahr et al., 1993). Breast cancer has much in common with HFI. Both are primarily female phenomena; both rise dramatically in frequency after menopause; both are associated with obesity and parity; both are modern phenomena; and both the frontal bone and breast are known to be target tissues for hormones such as estrogen and progesterone (Korenman, 1980). Since there is strong evidence that increased and/or prolonged estrogen stimulus is associated with an elevated risk of breast cancer in humans (Zumoff, 1981), this may also be the cause of HFI. Age at menarche and the cumulative number of ovulatory cycles are considered to be major determinants of breast cancer risk (Henderson et al., 1985). Historic populations rarely manifest HFI since they were exposed to different men-

strual and ovulatory patterns during adolescence and young adulthood. Menarche started at a later age and the onset of menopause was earlier. Historic females spent much of their reproductive period either pregnant or nursing. This implies minimal estrogen exposure. Our hypothesis explains not just the rarity of HFI in historic populations, but also why males with atrophied testes manifest an advanced type of HFI. The cause that brought change in female life cycle and longevity (and indirectly an increase in HFI frequency) was probably the "industrial revolution" (ca. 1760). Rapid urbanization reshaped the demographic characteristics of human populations, and consequently a new pattern of health and diseases emerged.

The issue of morphogensis and etiology can be analyzed from a different perspective. Perhaps the increased distance between the frontal lobe and endocranial surface in individuals with HFI yields to direct changes in cranial vascularization or to indirect changes through altered autonomic nerve function. Autonomic denervation impairs osteoblastic activity. Neuropeptides and vasoactive intestinal peptides (Bjurholm et al., 1988) both inhibit the effect of parathormone on osteoblasts. Vascular alterations could reduce these peptide levels, thereby allowing exaggerated, localized bone remodeling.

Another potential etiological hint derives from the notion that endocranial plate alterations in HFI appear to mimic those reported in the cortical bone of individuals suffering from hyperparathyroidism (e.g., Bennett, 1971). Parathormone works by inducing a "second messenger" which alters cyclic AMP (cAMP) release (Bjurholm et al., 1988; Greenfield et al., 1996). Neuropeptide Y, vasoactive intestinal peptide (VIP), and interleukin-6 (IL-6) also alter cAMP release. Curiously, both the parathormone and VIP effects on cAMP are IL-6-dependent processes. Could a locally active phenomenon, not parathyroid hormone, induce the same "second messenger?" Neuropeptides and VIPs (Bjurholm et al., 1988) both inhibit the effect of parathormone on osteoblasts. Vascular alteration could reduce these peptide levels. In their absence, parathormone could stimulate bone resorption by inducing osteoblasts to secrete interleukin-6, which in turn would stimulate osteoclast activity (Greenfield et al., 1996).

CONCLUSIONS

1. There is no reason to relate the HFI phenomenon to any specific syndrome, as some earlier workers had done (Morel, 1930; Stewart, 1928; Calame, 1951). Since HFI is common in elderly females, almost any association (e.g., osteoporosis, sterility) can be demonstrated. In this respect we agree with Perou (1964) that "HCI is a pathological condition representing a phenomenon in itself" (p. 79). Nevertheless, we disagree with Perou (1964) that HFI is a genetically-based developmental disease with endocrine imbalance and mental disturbance.
2. There is great ambiguity about HFI in the medical literature. Caution should be applied when using data from medical publications, since much has been based upon X-ray analysis, which is of limited value in the analysis of HFI.
3. HFI can appear in different ways: each is the result of the same process and probably of the same etiology. In the past, investigators failed to recognize the mild stages of HFI (types A and B) as an early part of the general HFI process. This led to false statistics and erroneous interpretations of the observations.
4. HCD should be considered as a separate phenomenon, even when it appears in association with HFI.
5. To facilitate the description of cranial hyperostoses, uniform terminology (HFI, HCD) has been recommended. The term HCI is too general and should not be used instead of HFI.
6. HFI is a modern phenomenon (19th–20th centuries), rarely seen in historic populations, regardless of geographical origin. The "turning point" in HFI frequency is probably the "industrial revolution."
7. HFI is not a purely female phenomenon. Its magnitude of manifestation and frequency, however, are much higher in the female population.

8. HFI begins in the endocranial plate and later involves the periosteal part of the dura. The diploe and ectocranial plate are not involved.
9. Probably only males with hormonal disturbance (e.g., atrophic testis) will manifest HFI type D.
10. HFI is an age phenomenon in the sense that: a) it is much less frequent in females under 40 years of age, and b) although advanced cases of HFI (types C and D) may appear as early as age 40 years, they are more frequently found after age 60 years. The frequency of HFI type D will not increase from age 50.
11. The frequency of HFI does not vary between African Americans and European Americans.
12. It is hypothesized that prolonged estrogen stimulus during the reproductive period may be the primary factor contributing to the greater frequencies of HFI seen in modern (i.e., 20th century) samples of postmenopausal females.

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